Duke | OFFICE of AUDIT, RISK & COMPLIANCE

Human Subject Research Compliance
Final Compliance Review Summary

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Title of Study: Omega-3 Supplementation for Co-Morbid Depression and Heart Failure Treatment
IRB Protocol #: Pro00042272
Principal Investigator: Wei Jiang, MD
Clinical Research Unit: Psychiatry

Date of Final Summary: October 8, 2015

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Executive Summary

The Duke Office of Audit, Risk and Compliance, Human Subject Research Compliance (HSRC) section has conducted a routine compliance review to: 1) assess adherence to the Institutional Review Board (IRB) approved study protocol, Good Clinical Practices (GCP) guidelines, and State and Federal Regulations; 2) determine that the rights and welfare of human research subjects are being or have been adequately protected by the Investigator and his research staff; and 3) assess the integrity of the study data. This routine compliance review was performed per the HSRC Review Standard Operating Procedure.

The following documents were analyzed in the course of this review:

- IRB approved research protocols
- IRB approved consent form documents
- All IRB amendments/addendums
- A chronological summary of the dates of IRB actions
- Regulatory files
- Pre-screening process
- Consent Process and all Informed Consent Forms
- Clinical charts/medical records
- Site and IRB Correspondence
- Curriculum Vitae, Licensure and Training Regulatory files
- Investigational Drug Services
- Other supporting documentation

Study-specific regulatory files, ten subject files, 109 consents and appropriate source documentation were reviewed.

Study synopsis

The OCEAN trial is a prospective, randomized, double-blind, placebo-controlled 3-arm pilot study to test the effects of two omega 3 supplements, compared with placebo, on depression, plasma omega 3 concentration changes, and their association with depression in 108 patients with chronic heart failure and moderate-to-severe comorbid major depressive disorder.[1]

The protocol has received no prior Food and Drug Administration (FDA) or Duke Office of Audit, Risk and Compliance, HSRC section reviews.

Wei Jiang, MD is the Principal Investigator (PI) for this study and is responsible for all regulatory and procedural elements of the study. The primary Clinical Research Coordinator (CRC) for this study is Jennifer Wilson. Additional key personnel include: Joseph Rogers, MD,

[1] IRB approved protocol, version date March 25, 2014, section 5, p. 16.

and Chetan Patel, MD (Co-Principal Investigator); Michael Babyak, PhD (Statistician); and Stephen Boyle, PhD (Other).

The study is sponsored by the National Institute of Mental Health (NIMH) and Ocean Nutrition Canada.

The first study subject for this clinical trial was screened on May 28, 2014. The IRB has approved enrollment for 120 subjects. At the time of this review, the site had consented 79 subjects. To date, 11 subjects have completed the study, seven remain active, two subjects have withdrawn, and the remaining 59 subjects are pending enrollment into the trial. The study is open to enrollment. There has been one adverse event reported to the IRB. There has been one reported protocol deviation/violation since the inception of this study.

This study is registered on the www.clinicaltrials.gov website.

The review concluded that the action items listed below are appropriate. Please provide the Duke Office of Audit, Risk and Compliance, HSRC section with copies of your response to the Action Plan by October 30, 2015. A review completion letter will be issued for this compliance review once all action items have been completed and verified by our office.

Observations and Action Plans

Issue

1. Observation: During the initial review of the Signature and Delegation of Authority log, study responsibilities were not listed for the following individuals:

Wei Jiang, MD	Michael Babyak, PhD	Joseph Rogers, MD
Stephen Boyle, PhD	Chetan Patel, MD	

In addition, the following individuals who were listed as key personnel in the eIRB were not listed on the Signature and Delegation of Authority log:

Christopher O'Connor, MD	Kaitlyn Weinberg	Sharon Minda

Further, the following issues were identified as missing or incomplete:

- Initials were missing for Joseph Rogers, MD
- A study role was not listed for Julia Sun
- PI initials and date were missing for all key personnel listed
- Start and end dates, if applicable, were not listed

Per GCP 4.1.5, "the investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties."[2]

[2] 2012 Code of Federal Regulations & ICH Guidelines GCP Reference Guide, April 1, 2012, p.263

Action Plan: Please update the Site Staff Delegation and Signature Log to reflect the names, signatures, responsibilities, start and end dates of all individuals who should be considered key personnel for this study. If signatures cannot be obtained, please create a memo to file detailing this.

Please submit a protocol deviation to the IRB regarding the performance of study activities without proper authorization by the PI. Please outline the details of the deviation as noted above and maintain a copy of this deviation in the regulatory binder for this study. When submitting the deviation, please include what actions have been taken to address this issue and what actions will be taken in the future to prevent such instances from recurring. Please provide documentation of the submission, as well as the IRB response, to the Duke Office of Audit, Risk and Compliance, HSRC section. Please also provide the updated Site Staff Delegation and Signature Log to the Duke Office of Audit, Risk and Compliance, HSRC section.

Expected Completion Date : October 30, 2015

Actual Completion Date :

Issue

2. Observation: Per the protocol, blood samples will be collected at certain intervals and stored at -70ºC at the individual study sites until they can be batch shipped under dry ice to a core laboratory.[3]

Samples of subjects who consented to blood draws were found in a locked -70ºC freezer. However, a record of the daily freezer temperature could not be located in order to verify that the integrity of the samples had been maintained.

Action Plan: Please verify that the necessary temperature was maintained for the samples currently located in the freezer in order to ensure sample integrity. Please provide documentation of the verification to the Duke Office of Audit, Risk and Compliance, HSRC section.

If it cannot be determined that the samples have been stored as required by the protocol, please submit a protocol deviation to the IRB. Please outline the details of the deviation as noted above and maintain a copy of this deviation in the regulatory binder for this study. When submitting the deviation, please include what actions have been taken to address this issue and what actions will be taken in the future to prevent such instances from recurring. Please provide documentation of the submission, as well as the IRB response, to the Duke Office of Audit, Risk and Compliance, HSRC section.

Going forward, please maintaining a freezer temperature log or documentation that the freezer is being monitored as verification that the samples are maintained at the protocol-specified temperature.

[3] IRB approved protocol, version date March 25, 2014, section 7.5.1, p. 23.

Expected Completion Date : October 30, 2015

Actual Completion Date :

Issue

3. Observation: Per GCP 4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s).[4] During the review of study drug accountability, it was noted that Subject 001-106 did not return the study drug bottle including any unused medication at his last follow-up visit. The study coordinator contacted the subject and he does not think he has it any longer. He believes he left the bottle at the hospital during his inpatient stay. The subject agreed to contact the study coordinator if he locates any unused study drug.

Action Plan: Please submit a protocol deviation to the IRB for the incomplete accountability for the study drug taken by Subject 001-106. Please outline the details of the deviation as noted above and maintain a copy of this deviation in the regulatory binder for this study. When submitting the deviation, please include what actions have been taken to address this issue and what actions will be taken in the future to prevent such instances from recurring. Please provide documentation of the submission, as well as the IRB response, to the Duke Office of Audit, Risk and Compliance, HSRC section.

Expected Completion Date : October 30, 2015

Actual Completion Date :

Issue

4. Observation: Per GCP 4.1.5, "the investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority (ies), and which was given approval/favorable opinion by the IRB/IEC."[5]

- Subject 001-101 did not complete the six-minute walk, the PSS, or the blood draw during the Screening/Baseline/Randomization visit
- Subject 001-104 missed the Week 2 and Week 10 phone calls
- Subject 001-106 did not complete the six-minute walk during the Screening/Baseline/Randomization visit
- Subject 001-109 did not complete the six-minute walk or the CIRS during the Screening/Baseline/Randomization visit

[4] 2012 Code of Federal Regulations & ICH Guidelines GCP Reference Guide, April 1, 2012, p.265.
[5] 2012 Code of Federal Regulations & ICH Guidelines GCP Reference Guide, April 1, 2012, p.263.

- Subject 001-112 did not complete the BDI-II during the Week 2 and Week 6 phone call; the STAI-1 was not completed during the Week 6 phone call
- Subject 001-115 did not complete the GHQ, KCCQ, CIRS, STAI-1, STAI-2, SF-36 or PSS at the Screening/Baseline/Randomization visit; the BDI-II was not completed during the Week 2 phone call or Week 12 visit; the KCCQ, six-minute walk, CIRS, STAI-2, SF-36 and PSS were not completed at the Week 12 visit.
- Subject 001-116 missed the Week 2 phone call and did not complete the BDI-II and STAI-1 during the Week 6 phone call

Action Plan: Please review all subjects consented and not a part of this compliance review sample selection to determine if there are any additional instances of tests/procedures that have occurred outside the protocol specified window or tests/procedures that have not been completed per the protocol.

Please submit a protocol deviation to the IRB for the above instances where the protocol was not followed as written. Please outline the details of the deviation as noted above and maintain a copy of this deviation in the regulatory binder for this study. When submitting the deviation, please include what actions have been taken to address these issues and what actions will be taken in the future to prevent such instances from recurring. Please provide documentation of the submission, as well as the IRB response, to the Duke Office of Audit, Risk and Compliance, HSRC section.

Expected Completion Date : October 30, 2015

Actual Completion Date :

Issue

5. Observation: Per the protocol, inclusion criteria for the study includes an NYHA Class >=II.[6] Subject 001-118 who signed consent on May 13, 2015 had an NYHA class of I noted on a History and Physical dated May 13, 2015 in Maestro Care. Subject 001-111 who signed consent on November 14, 2014 had an NYHA class of I noted in a Progress Note dated November 14, 2014 in Maestro Care. Subject 001-109, possibly consented on August 7, 2014 did not have an NYHA class noted.

Action Plan: Please carefully review the subjects listed above against the eligibility criteria to determine if they are indeed qualified to participate in the study.

If any of these subjects are not qualified to participate, please submit a protocol deviation to the IRB detailing the inclusion of subjects who do not meet the inclusion criteria for the study. Please outline the details of the deviation as noted above and maintain a copy of this deviation in the regulatory binder for this study. When submitting the deviation, please include what actions have been taken to address this event and what actions will be taken in the future to prevent such instances from recurring. Please provide documentation of the submission, as well as the IRB response, to the Duke Office of Audit, Risk and Compliance, HSRC section.

[6] IRB approved protocol, version date March 25, 2014, section 6.1, p. 20.

Expected Completion Date : October 30, 2015

Actual Completion Date :

Issue

6. Observation: Of the 109 consents reviewed for this study, there was one subject consent that was obtained using an incorrect version date.

Subject ID:	Date of Consent:	Version Date Used:	Version Date Should Have Used:
SF/T-S	June 4, 2015	June 4, 2014	June 3, 2015

In addition, the following informed consent form issues were identified:

Subject Number	Date of Consent	Consent Form Issue
001-105	August 17, 2014	Time not documented with subject's signature.
001-105	August 26, 2014	Year not included in date with subject's signature.
001-109	August 7, 2014 (per consent note)	Date and time are not included with the subject or the person obtaining consent's signature.
SF/R-W	June 17, 2014	Year not included in date with subject's signature.

Action Plan: Please review the above informed consent documentation issues and create memos to file to explain the events listed above. Please place a copy of the memos to file in the research chart for each affected subject, as well as forward copies of the memos to the Duke Office of Audit, Risk and Compliance, HSRC section.

For screen failure subject T-S, please create a memo to file regarding the use of an unapproved version of the consent form and place it in the subject's research chart. Please cite the differences between the version used and the version date required. A protocol deviation is not warranted if the changes appear to be minor administrative changes that did not adversely affect the subjects' rights, integrity or welfare. If there are more than minor administrative changes, a protocol deviation will need to be filed with the IRB. When submitting the deviation, please include what actions have been taken to address this issue and what actions will be taken in the future to prevent such instances from recurring. Please provide documentation of the submission, if required, as well as the IRB response, to the Duke University Office of Audit, Risk and Compliance, HSRC section.

Going forward, please print all consent forms directly from the section of the eIRB website entitled: *Approved and Watermarked Consent Forms.* This ensures that the study document has been subject to IRB review and given approval/favorable opinion per GCP 8.2.7.[7]

Expected Completion Date : October 30, 2015

Actual Completion Date :

Conclusion

Wei Jiang, MD demonstrated knowledge of the protocol and study requirements. She was aware of her responsibilities as a PI under the regulations and guidelines for the conduct of research trials and demonstrated that she was an integral part of the study and safety review process. The research team demonstrated commitment towards the conduct of their research and the importance of conducting a study, which adheres to safe clinical practices and ethical standards. The IRB protocols, consent forms and additional IRB related documents were reviewed in advance of the on-site documentation review.

Please contact the Duke Office of Audit, Risk and Compliance, HSRC section if we can further assist you.

Human Subject Research Compliance section
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[7] 2012 Code of Federal Regulations & ICH Guidelines GCP Reference Guide, April 1, 2012, p.298.